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# Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC Study

Gabriel D. Shapiro [a,b], Linda Dodds [c,*], Tye E. Arbuckle [d], Jillian Ashley-Martin [c], Adrienne S. Ettinger [e], Mandy Fisher [d], Shayne Taback [f], Maryse F. Bouchard [b], Patricia Monnier [a], Renée Dallaire [g], Anne-Sophie Morisset [g], William Fraser [b,h,i]

[a] McGill University, Montreal, QC, Canada
[b] CHU Sainte-Justine Research Centre, Université de Montréal, Montreal, QC, Canada
[c] Dalhousie University, Halifax, NS, Canada
[d] Health Canada, Ottawa, ON, Canada
[e] Yale University, New Haven, CT, USA
[f] University of Manitoba, Winnipeg, MB, Canada
[g] Laval University, Québec City, QC, Canada
[h] Centre de recherche du CHUS, Sherbrooke, QC, Canada
[i] Université de Sherbrooke, Sherbrooke, QC, Canada

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ABSTRACT

*Background:* Studies report increases in rates of gestational diabetes mellitus (GDM) over recent decades. Environmental chemicals may increase the risk of diabetes through impacts on glucose metabolism, mitochondrial dysfunction, and endocrine-disrupting mechanisms including effects on pancreatic β-cell function and adiponectin release.

*Objectives:* To determine the associations between pesticides, perfluoroalkyl substances (PFASs) and polychlorinated biphenyls (PCBs) measured in early pregnancy and impaired glucose tolerance (IGT) and GDM in a Canadian birth cohort.

*Methods:* Women enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study were included if they had a singleton delivery and did not have pre-existing diabetes. Exposure variables included three organophosphorus (OP) pesticide metabolites detected in first-trimester urine samples, as well as three organochlorine (OC) pesticides, three PFASs, and four PCBs in first-trimester blood samples. Gestational IGT and GDM were assessed by chart review in accordance with published guidelines. Adjusted logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for the association between quartiles of environmental chemicals and both gestational IGT and GDM.

*Results:* Of the 2001 women recruited into the MIREC cohort, 1274 met the inclusion criteria and had outcome and biomonitoring data available. Significantly lower odds of GDM were observed in the third and fourth quartiles of dimethylphosphate (DMP) and in the fourth quartile of dimethylthiophosphate (DMTP) in adjusted analyses (DMP Q3: OR=0.2, 95% CI=0.1–0.7; DMP Q4: OR=0.3, 95% CI=0.1–0.8; DMTP: OR=0.3, 95% CI=0.1–0.9). Significantly elevated odds of gestational IGT was observed in the second quartile of perfluorohexane sulfonate (PFHxS) (OR=3.5, 95% CI=1.4–8.9). No evidence of associations with GDM or IGT during pregnancy was observed for PCBs or OC pesticides.

*Conclusions:* We did not find consistent evidence for any positive associations between the chemicals we examined and GDM or IGT during pregnancy. We observed statistical evidence of inverse relationships between urine concentrations of DMP and DMTP with GDM. We cannot rule out the influence of residual

*Abbreviations:* CHMS, Canadian Health Measures Survey; DDE, p,p′-dichlorodiphenyldichloroethylene; DEP, diethylphosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; LOD, limit of detection; MIREC, Maternal-Infant Research on Environmental Chemicals; OC, organochlorine; OP, organophosphorus; OR, odds ratio; PCB, polychlorinated biphenyl; PCB118, 2,3′,4,4′,5-pentachlorobiphenyl; PCB138, 2,2′,3,4,4′,5′-hexachlorobiphenyl; PCB153, 2,2′,4,4′,5,5′-hexachlorobiphenyl; PCB180, 2,2′,3,4,4′,5,5′-heptachlorobiphenyl; PFAS, perfluoroalkyl substance; PFHxS, perfluorohexane sulfonate; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate

* Correspondence to: Perinatal Epidemiology Research Unit, 7th Floor Women's Site, IWK Health Centre, 5980 University Ave., PO Box 9700, Halifax, NS, Canada B3H 6R8.
*E-mail address:* L.Dodds@dal.ca (L. Dodds).

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confounding due to unmeasured protective factors, such as nutritional benefits from fruit and vegetable consumption, also associated with pesticide exposure, on the observed inverse associations between maternal OP pesticide metabolites and GDM. These findings require further investigation.



## 1. Introduction

Diabetes is a substantial and growing public health problem (International Diabetes Federation, 2013), and increasing rates of gestational diabetes mellitus (GDM) form part of this trend (Davenport et al., 2010; Feig et al., 2014; Galtier, 2010). Evidence suggests that the etiology of diabetes is likely multifactorial (Public Health Agency of Canada, 2011) and that environmental chemicals may play a role along with more traditional risk factors such as excess caloric consumption, lack of physical activity and increased BMI (Bezek et al., 2008; Kuo et al., 2013; Thayer et al., 2012). However, examination of the environmental chemical hypothesis with regards to GDM has been more limited (Ettinger et al., 2009; Robledo et al., 2013; Saldana et al., 2007; Saunders et al., 2014). The potential health effects of perinatal chemical exposures (Newbold, 2011) and GDM (Aerts and Van Assche, 2006; Osgood et al., 2011) are a concern for subsequent maternal and offspring metabolic health.

Organophosphates (OPs) are the most widely used class of pesticides for agricultural and landscape pest control (Rezg et al., 2010). The primary route of exposure is via ingestion of contaminated food (Lu et al., 2008). These pesticides are metabolized relatively quickly and are not persistent in the environment (Lambert et al., 2005). The dialkyl phosphate metabolites, rather than the parent compounds, are used as non-specific biomarkers of exposure in urine. Evidence from human and animal studies supports a potential role for OPs in the development of obesity and type 2 diabetes (Rahimi and Abdollahi, 2007; Rezg et al., 2010).

Epidemiologic studies have also shown associations between organochlorine (OC) pesticides and diabetes (Azandjeme et al., 2014; Cox et al., 2007; Gray et al., 2013; Hectors et al., 2011; Lee et al., 2011a; Philibert et al., 2009; Rignell-Hydbom et al., 2009, 2007; Son et al., 2010; Turyk et al., 2009a, 2009b; Ukropec et al., 2010). While OC pesticides are no longer registered for use in Canada, they are persistent in the environment, and trace amounts may still be found in food products. Finally, epidemiologic evidence also suggests a potential role for other classes of chemicals including perfluoroalkyl substances (PFASs) (Lin et al., 2009; Steenland et al., 2010; Zhang et al., 2015) and polychlorinated biphenyls (PCBs) (Carpenter, 2008; Everett et al., 2011) in the development of diabetes.

The above-mentioned chemical classes are hypothesized to increase risk of diabetes through modulation of glucose metabolism (OP compounds and PFAS) (Hectors et al., 2011; Lv et al., 2013; Rahimi and Abdollahi, 2007), mitochondrial dysfunction (OC pesticides and PCBs) (Lee et al., 2014), and endocrine-disrupting mechanisms (OC pesticides and PCBs) (Lee et al., 2014) including effects on pancreatic β-cell function (PCBs) (Gray et al., 2013; Hectors et al., 2011) and adiponectin release (OC compounds) (Howell and Mangum, 2011). However, exploration of these chemicals in relation to GDM has been limited (Saldana et al., 2007; Saunders et al., 2014). In light of the current literature, we speculated that exposure to the above-mentioned chemical classes may be associated with GDM or impaired glucose tolerance (IGT) during pregnancy. Using data from a Canadian birth cohort, the present study sought to determine whether exposure to OP or OC pesticides, PFAS or PCBs, measured early in pregnancy in maternal blood and urine, was associated with increased risk of GDM or IGT during pregnancy.

## 2. Materials and methods

### 2.1. Study sample

The Maternal-Infant Research on Environmental Chemicals (MIREC) Study is a longitudinal birth cohort study conducted in Canada. Further details concerning inclusion and exclusion criteria and study objectives and procedures have been published elsewhere (Arbuckle et al., 2013). The present analysis used the same subset of the MIREC study sample as our previous work looking at GDM and gestational IGT in relation to metals and phthalates (Shapiro et al., 2015). Briefly, participants were included if they gave birth to a live singleton, had sufficient data from the glucose challenge test (GCT) and/or oral glucose tolerance test (OGTT) to determine a diagnosis of GDM and gestational IGT, and had exposure data available for at least one of the chemicals investigated (PCBs, OC pesticides, OPs, and PFASs). All participants signed informed consent forms and the study received ethical approval from Health Canada and all the study centres.

### 2.2. Chemical Biomonitoring data

First trimester urine samples were analysed for six OP pesticide metabolites (diethylphosphate (DEP), diethyldithiophosphate (DEDTP), diethylthiophosphate (DETP), dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP)). Eleven OC pesticides (p,p′-dichlorodiphenyldichloroethylene (DDE), oxychlordane, trans-nonachlor, aldrin, alpha-chlordane, gamma-chlordane, cis-onachlor, gamma-hexachlorocylcohexane (γ-HCH), p,p′-dichlorodiphenyltrichloroethane (p,p′-DDT), hexachlorobenzene (HCB), mirex)), three PFASs (perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS)), and 24 PCBs were measured in first trimester plasma samples. We focused our analyses on exposures for which there were detectable levels in $>75\%$ of subjects. This included three OP pesticide metabolites (DEP, DMP, DMTP), three OC pesticides (p,p′- DDE, oxychlordane, trans-nonachlor), all three PFASs and four PCB congeners (2,3′,4,4′,5-pentachlorobiphenyl (PCB118), 2,2′,3,4,4′,5′-hexachlorobiphenyl (PCB138), 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB153), 2,2′,3,4,4′,5,5′-heptachlorobiphenyl (PCB180)).

All chemical analyses were carried out at the Toxicology Centre of the Quebec Institute of Public Health (Institut national de santé publique du Québec), accredited by the Standards Council of Canada under ISO 17025 and CAN-P-43. The accuracy and precision of the analyses are evaluated on a regular basis through the laboratory's participation in external quality assessment programs (Arbuckle et al., 2013). OC pesticides and PCBs were analyzed by gas chromatography—mass spectrometry using the Agilent 6890N/5973. Plasma samples were enriched with internal standards and halogenated organic compounds were retrieved by liquid-liquid extraction with a mixture of ammonium sulfate:ethanol:hexane (1:1:3). Extracts were concentrated, automatically purified on florisil column and then analyzed by gas chromatography coupled

to a mass spectrometer. Measurements of ions generated after negative chemical ionization were performed in selective ion mode. PFASs were analyzed using the Waters Acquity UPLC-MS-MS. Analytes were extracted at alkaline pH with methyl tertbutyl ether and ion pairing with tetrabutylammonium hydrogensulfate, evaporated to dryness and dissolved in the mobile phase. They were then analyzed by UPLCMS-MS operated in the MRM mode with an electrospray ion source in negative mode. Concentrations below the limit of detection (LOD) were substituted as one half the LOD.

### 2.3. Impaired glucose tolerance in pregnancy and gestational diabetes mellitus

Gestational IGT and GDM were assessed by chart review based on the results of a 50 g glucose challenge test (GCT) and 75 or 100 g oral glucose tolerance test (OGTT), in accordance with guidelines from the Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada (Berger et al., 2002; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008). The algorithm used to calculate gestational IGT and GDM is described in our previous work with this cohort (Shapiro et al., 2015). Briefly, gestational IGT was diagnosed if one of the OGTT cut-off values was met or exceeded, whereas GDM required at least 2 values at or above the cut-off values.

### 2.4. Statistical analyses

Descriptive statistics for maternal demographic and clinical characteristics were calculated according to study outcomes (normal blood glucose, gestational IGT, GDM) using frequency distributions and chi-square tests of significance. Geometric means and standard deviations were calculated for chemical concentrations according to study outcomes. In determining the geometric mean, concentrations of OP pesticide metabolites were adjusted for urinary specific gravity (SG) according to the following formula: $P_c = P_i\ [(SG_m - 1)/(SG_i - 1)]$, where $P_c$=SG-adjusted metabolite concentration (μg/ml), $P_i$=observed metabolite concentration, $SG_i$=specific gravity of the urine sample, and $SG_m$=median SG for the cohort (Just et al., 2010).

All contaminant concentrations were grouped into quartiles for analyses, and logistic regression models were used to examine associations between quartiles and study outcomes. In calculating odds ratios for these outcomes, we examined subjects with GDM vs. normal blood glucose, gestational IGT vs. normal glucose, and subjects with either gestational IGT or GDM grouped together vs. normal blood glucose. In addition to the individual contaminants, we also examined the summed molar concentrations of dimethyl OP metabolites (DMP and DMTP) (Arcury et al., 2006), the sum of all PCBs, sum of non-dioxin-like PCBs (PCBs 138, 153 and 180), and the PCB mixture Aroclor 1260 (calculated by multiplying the sum of the wet weight concentration of PCBs 153 and 138 by 5.2 (Health Canada, 2010)).

We examined the following maternal variables as potential confounders: age at delivery, pre-pregnancy BMI ($<25$, 25-29.9, $\geq 30$ kg/m$^2$), parity (nulliparous vs. parous), household income ($\leq$ $30,000, 30,001–50,000, 50,001–100,000, $>$ 100,000), education (high school diploma or less, some college or trade school, undergraduate university degree, graduate university degree), race (White, non-White), and smoking (never or quit before pregnancy, quit when knew pregnant, current smoker). Variables were selected *a priori* for inclusion in multivariable models on the basis of association with gestational IGT and GDM in univariate analyses ($p < 0.1$) or on the basis of evidence of an association from the literature. Specific gravity was included as a covariate in all adjusted models for OP pesticide metabolites to account for heterogeneity in urinary dilution (Arbuckle et al., 2014). Total lipids were included as a covariate in all adjusted models for PCBs and OC pesticides (Schisterman et al., 2005). In light of collinearity between income and education, and as model results were not substantially different with adjustment for both income and education vs. adjustment for education only, we did not adjust for income in the final models.

For models with statistically significant associations, we used restricted cubic spline analysis to further examine the dose-response relationship (Desquilbet and Mariotti, 2010). This technique is applicable when there is no *a priori* hypothesis regarding the shape of the dose-response association, and it overcomes inherent limitations of our categorical analyses. Knots were set at the 5th, 50th, and 95th percentiles and the referent value was set to the 5th percentile. Regression analyses were carried out using IBM-SPSS for Windows version 20 and spline analyses were carried out using SAS 9.4.

## 3. Results

Of the 2001 women recruited, 18 withdrew and asked that all their data and biospecimens be destroyed (0.9%). Of the remaining 1983 subjects, 97 in total were excluded (4.9%) because of a multiple pregnancy (n=48), stillbirth (n=21), pre-existing diabetes (n=24), or having no biological samples available for the measurement of any of the contaminants of interest (n=4), leaving 1886 subjects. Of these, information from a GCT or OGTT was available to calculate the study outcomes for 1274 women (67.6%). Excluded participants were slightly less likely to be obese (10.3% vs. 15.0% of included participants, p=.05) and slightly more likely to report being White (88.1% vs. 84.5%, p=.04) and to be current smokers (7.5% vs. 4.4%, p=.04).

Table 1 shows the characteristics of the study sample. Participants were between the ages of 18 and 49 (mean (SD)=33.0 (4.9) years), with 40% aged 35 or older. Twenty percent of participants were overweight before becoming pregnant and 15% were obese.

**Table 1**
Study sample characteristics (N=1274).

| Variable | | n (%) |
|---|---|---|
| Age | ≤29 | 308 (24.2) |
| | 30–34 | 447 (35.1) |
| | ≥35 | 515 (40.4) |
| | Missing | 4 (0.3) |
| Pre-pregnancy BMI (kg/m$^2$) | Underweight or Normal (<25)[a] | 752 (59.0) |
| | Overweight (25–29.9) | 257 (20.2) |
| | Obese (≥30) | 191 (15.0) |
| | Missing | 74 (5.8) |
| Parity | Nulliparous | 563 (44.2) |
| | Parous | 709 (55.7) |
| | Missing | 2 (0.2) |
| Education | High school diploma or less | 106 (8.3) |
| | Some college, or trade school | 352 (27.6) |
| | Undergraduate university degree | 477 (37.4) |
| | Graduate university degree | 338 (26.5) |
| | Missing | 1 (0.1) |
| Household Income ($CAD) | ≤50,000 | 209 (16.4) |
| | 50,001–100,000 | 505 (39.6) |
| | ≥100,000 | 506 (39.7) |
| | Missing | 54 (4.2) |
| Race | White | 1077 (84.5) |
| | Non-White | 197 (15.5) |
| Smoking | Never or quit before pregnancy | 1124 (88.2) |
| | Quit when knew pregnant | 93 (7.3) |
| | Current smoker | 56 (4.4) |
| | Missing | 1 (0.1) |

[a] Underweight and Normal BMI were combined because of the small number of underweight participants (34 (2.7%)).

**Table 2**
Geometric mean of organophosphorus pesticide metabolites, organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls by GDM and gestational IGT outcomes.

| Chemical (μg/L) | LOD | % > LOD[a] | Total N[b] | Geometric Mean (SD) | | |
|---|---|---|---|---|---|---|
| | | | | Normal glucose N=1167 | Gestational IGT cases N=48 | GDM cases N=59 |
| **Organophosphorus pesticide metabolites[c]** | | | | | | |
| Diethylphosphate (DEP) | 1.00 | 77.8 | 1247 | 2.50 (2.33) | 2.55 (2.67) | 2.28 (2.42) |
| Dimethylphosphate (DMP) | 1.00 | 79.8 | 1246 | 3.34 (2.68) | 2.18 (2.94) | 2.22 (2.53) |
| Dimethylthiophosphate (DMTP) | 0.60 | 81.0 | 1245 | 3.64 (3.94) | 2.25 (5.23) | 2.18 (3.52) |
| **Organochlorine pesticides** | | | | | | |
| *p,p′*-Dichlorodiphenyldichloroethylene (DDE) | 0.09 | 98.2 | 1250 | 0.36 (2.36) | 0.47 (2.90) | 0.32 (1.95) |
| Oxychlordane | 0.005 | 90.8 | 1249 | 0.012 (1.919) | 0.012 (1.926) | 0.012 (2.030) |
| Trans-Nonachlor | 0.01 | 84.0 | 1249 | 0.017 (1.968) | 0.019 (2.161) | 0.017 (2.121) |
| **Perfluoroalkyl substances** | | | | | | |
| Perfluorooctanoic acid (PFOA) | 0.10 | 99.8 | 1259 | 1.68 (1.80) | 1.70 (1.73) | 1.64 (1.64) |
| Perfluorooctane sulfonate (PFOS) | 0.30 | 99.8 | 1259 | 4.58 (1.81) | 4.29 (1.60) | 4.74 (1.67) |
| Perfluorohexane sulfonate (PFHxS) | 0.20, 0.30 | 96.1 | 1259 | 1.02 (2.31) | 1.00 (1.79) | 1.05 (2.03) |
| **Polychlorinated biphenyls** | | | | | | |
| 2,3′,4,4′,5-Pentachlorobiphenyl (PCB118) | 0.01 | 74.7 | 1250 | 0.014 (2.057) | 0.015 (2.088) | 0.014 (2.091) |
| 2,2′,3,4,4′,5′-Hexachlorobiphenyl (PCB138) | 0.01 | 92.9 | 1250 | 0.026 (2.118) | 0.028 (2.135) | 0.025 (2.223) |
| 2,2′,4,4′,5,5′-Hexachlorobiphenyl (PCB153) | 0.01 | 97.9 | 1250 | 0.047 (2.129) | 0.048 (2.218) | 0.044 (2.212) |
| 2,2′,3,4,4′,5,5′-Heptachlorobiphenyl (PCB180) | 0.01 | 92.2 | 1250 | 0.030 (2.371) | 0.030 (2.271) | 0.029 (2.470) |
| Aroclor 1260 | 0.10 | 98.1 | 1250 | 0.381 (2.112) | 0.396 (2.152) | 0.365 (2.157) |

[a] The following chemicals had less than 75% of the samples above the LOD and were excluded from further analyses: Organophosphorus pesticide metabolites: Diethylthiophosphate (DETP), Diethyldithiophosphate (DEDTP), Dimethyldithiophosphate (DMDTP); Organochlorine Pesticides: Aldrin, alpha-Chlordane, gamma-Chlordane, cis-Nonachlor, gamma-Hexachlorocylcohexane (γ-HCH), p,p′-Dichlorodiphenyltrichloroethane (p,p′-DDT), Hexachlorobenzene (HCB), Mirex; PCBs: 28, 52, 66, 74, 99, 101, 105, 128, 146, 156, 163, 167, 170, 178, 183, 187, 194, 201, 203, 206.
[b] Number of subjects with data available for each exposure.
[c] Geometric mean concentrations for organophosphorus pesticide metabolites are adjusted for urinary specific gravity.

More than 60% of participants had an undergraduate university degree, and more than a quarter had a graduate degree. Forty percent of participants had an annual household income of at least $100,000 Canadian, while only 16% had household income below $50,000. Fifteen percent of participants reported non-White race, and less than 5% of study subjects smoked during pregnancy. Forty-eight participants (3.8%) were identified as GDM cases and 59 (4.6%) were identified as having gestational IGT. The distribution of maternal characteristics by diabetes status has been described in our previous work (Shapiro et al., 2015). As expected, GDM and gestational IGT cases were more likely to be overweight or obese compared to subjects with normal blood glucose.

Table 2 shows the percentage of samples above the LOD and the geometric mean for each chemical analyzed, stratified by the three outcome categories (normal blood glucose, gestational IGT, GDM). Pearson correlations (data not shown) between OP pesticide metabolites ranged from .26 (DEP and DMTP) to .66 (DMP and DMTP). Correlations among OC pesticides ranged from .39 (DDE and oxychlordane) to .82 (oxychlordane and trans-nonachlor). Among PFASs, correlations ranged from .45 (PFOA and PFHxS) to .56 (PFOA and PFOS), while correlations among PCB congeners ranged from .65 (PCBs 118 and 180) to .96 (PCBs 138 and 153) (all p-values for correlations between different chemicals in each class were $<0.01$). Across chemical classes, the highest correlations observed were those between OC pesticides and PCBs, which ranged from 0.45 (DDE and PCB 180) to 0.59 (Transnonachlor and PCB 138). Correlations between PFAS and both PCBs and OC pesticides were below 0.3, and those between all other chemical classes were below 0.1.

Table 3 shows the crude and adjusted odds ratios of each of the study outcomes (GDM vs. normal glucose, gestational IGT vs. normal glucose, gestational IGT or GDM vs. normal glucose) by quartile of contaminant concentrations. In comparing odds of GDM in the upper three quartiles vs. the lowest quartile for OP pesticides, inverse associations were observed for DMP and DMTP. Associations were statistically significant for the third and fourth quartiles of dimethylphosphate (DMP) and for the fourth quartile of dimethylthiophosphate (DMTP) (DMP Q3: OR=0.2, 95% CI=0.1–0.7; DMP Q4: OR=0.3, 95% CI=0.1–0.8; DMTP: OR=0.3, 95% CI=0.1–0.9), with significant dose-response relationships observed across quartiles for both compounds. A similar pattern was observed for the combined GDM/IGT outcome. Evidence of inverse associations with the outcome of gestational IGT only were also observed for these two contaminants (p-value for trend=0.07 for DMP, 0.12 for DMTP). Significantly reduced odds of gestational IGT were also observed in the third quartile of DEP (OR=0.2, 95% CI=0.1–0.6).

A significant dose-response relationship was observed in the cubic spline model between dimethyl OP metabolites and odds of GDM (p=0.02 for both exposures) (Fig. 1). A test of the null hypothesis that the relationship between dimethyl metabolite levels and odds of GDM is linear was not rejected (p=0.19), suggesting a linear association. An association of borderline significance was observed in the cubic spline model for DEP and odds of gestational IGT (p=0.08), with statistical evidence of a non-linear association (p=0.03 for test of non-linearity) (Fig. 1).

In examining associations between PFASs and study outcomes, elevated odds of gestational IGT were observed in the second quartile of PFHxS (OR=3.5, 95% CI=1.4–8.9) in adjusted analyses. A similar pattern, but with an attenuated odds ratio, was observed for the combined GDM/IGT outcome (adjusted OR for second quartile=2.4, 95% CI=1.3–4.4). A cubic spline model testing the relationship between PFHxS and gestational IGT did not show significant evidence of an overall association (p=0.73) (Fig. 2). No evidence of associations with GDM or gestational IGT was observed for PCBs or OC pesticides (Table 3).

## 4. Discussion

In this longitudinal birth cohort study of Canadian women, we evaluated the associations between maternal concentrations of OP and OC pesticides, PFASs and PCBs with gestational IGT and GDM. After adjustment for potential confounding variables, we observed

**Table 3**
Odds ratios (95% CI) for GDM, gestational IGT, and GDM or gestational IGT by contaminant quartiles.

| Contaminant (μg/L) | | GDM (N=44) vs. Normal Glucose (N=1102)[a] | | Gestational IGT (N=49) vs. Normal Glucose (N=1102)[a] | | GDM or gestational IGT (N=93) vs. Normal Glucose (N=1102)[a] | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted OR[b] (95% CI) | Adjusted OR[c] (95% CI) | Unadjusted OR (95% CI) | Adjusted OR[c] (95% CI) | Unadjusted OR (95% CI) | Adjusted[c] OR (95% CI) |
| **Organophosphorus pesticide metabolites** | | | | | | | |
| DEP | Q1 (0.5–1.1) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (1.2–2.1) | 1.2 (0.5–2.9) | 1.1 (0.4–2.8) | 0.6 (0.3–1.4) | 0.5 (0.2–1.2) | 0.9 (0.5–1.6) | 0.7 (0.4–1.4) |
| | Q3 (2.2–4.5) | 1.0 (0.4–2.4) | 0.9 (0.3–2.5) | 0.3 (0.1–0.8) | 0.2 (0.1–0.6) | 0.5 (0.3–1.1) | 0.4 (0.2–0.9) |
| | Q4 (4.6–96) | 1.2 (0.5–2.8) | 1.2 (0.4–3.7) | 1.1 (0.6–2.3) | 0.8 (0.3–2.0) | 1.1 (0.7–2.0) | 0.9 (0.4–1.9) |
| | p-value[d] | | 0.85 | | 0.41 | | 0.58 |
| DMP | Q1 (0.5–1.2) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (1.3–3) | 1.0 (0.5–2.1) | 0.8 (0.4–1.8) | 0.6 (0.3–1.4) | 0.6 (0.2–1.3) | 0.8 (0.5–1.4) | 0.7 (0.4–1.2) |
| | Q3 (3.1–6.5) | 0.3 (0.1–0.9) | 0.2 (0.1–0.7) | 0.7 (0.3–1.5) | 0.5 (0.2–1.1) | 0.5 (0.3–0.9) | 0.3 (0.2–0.7) |
| | Q4 (6.6–190) | 0.5 (0.2–1.3) | 0.3 (0.1–0.8) | 0.6 (0.3–1.4) | 0.4 (0.2–1.1) | 0.6 (0.3–1.1) | 0.3 (0.2–0.7) |
| | p-value[d] | | < 0.01 | | 0.07 | | < 0.01 |
| DMTP | Q1 (0.3–0.99) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (1–3.4) | 0.8 (0.4–1.7) | 0.8 (0.3–1.7) | 1.3 (0.6–2.8) | 1.3 (0.6–2.9) | 1.0 (0.6–1.7) | 1.0 (0.6–1.8) |
| | Q3 (3.5–9.3) | 0.5 (0.2–1.2) | 0.5 (0.2–1.2) | 1.0 (0.4–2.3) | 0.9 (0.4–2.1) | 0.7 (0.4–1.3) | 0.6 (0.3–1.2) |
| | Q4 (9.4–420) | 0.4 (0.1–0.9) | 0.3 (0.1–0.9) | 0.6 (0.2–1.4) | 0.5 (0.2–1.4) | 0.4 (0.2–0.9) | 0.4 (0.2–0.8) |
| | p-value[d] | | 0.01 | | 0.12 | | 0.01 |
| Dimethyl OP metabolites (DMP and DMTP, nmol/L) | Q1 (2.5–26.4) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (26.5–58.7) | 0.5 (0.2–1.1) | 0.5 (0.2–1.1) | 1.5 (0.7–3.1) | 1.6 (0.7–3.3) | 0.9 (0.5–1.5) | 0.9 (0.5–1.6) |
| | Q3 (58.9–120.3) | 0.4 (0.2–1.0) | 0.5 (0.2–1.0) | 0.5 (0.2–1.3) | 0.5 (0.2–1.4) | 0.5 (0.2–0.9) | 0.5 (0.3–0.9) |
| | Q4 (120.4–1615.2) | 0.3 (0.1–0.8) | 0.3 (0.1–0.8) | 0.6 (0.2–1.4) | 0.7 (0.3–1.7) | 0.4 (0.2–0.8) | 0.5 (0.2–0.9) |
| | p-value[d] | | 0.01 | | 0.11 | | < 0.01 |
| **Organochlorine pesticides** | | | | | | | |
| DDE | Q1 (0.05–0.21) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.22–0.31) | 1.4 (0.6–3.5) | 1.4 (0.6–3.5) | 0.7 (0.3–1.6) | 0.7 (0.3–1.7) | 1.0 (0.5–1.8) | 1.0 (0.5–1.8) |
| | Q3 (0.32–0.49) | 0.7 (0.3–2.0) | 0.5 (0.2–1.6) | 1.0 (0.5–2.1) | 1.0 (0.4–2.2) | 0.9 (0.5–1.7) | 0.8 (0.4–1.5) |
| | Q4 (0.5–26) | 2.0 (0.9–4.7) | 1.1 (0.4–2.9) | 0.6 (0.3–1.5) | 0.6 (0.2–1.6) | 1.2 (0.7–2.1) | 0.8 (0.4–1.6) |
| | p-value[d] | | 0.74 | | 0.49 | | 0.43 |
| Oxychlordane | Q1 (0.003-0.009) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.009–0.013) | 1.2 (0.5–2.8) | 1.0 (0.4–2.4) | 0.8 (0.4–1.8) | 0.8 (0.3–1.7) | 0.9 (0.5–1.7) | 0.9 (0.5–1.6) |
| | Q3 (0.014–0.018) | 0.9 (0.3–2.4) | 0.8 (0.3–2.3) | 0.6 (0.2–1.5) | 0.6 (0.2–1.5) | 0.7 (0.4–1.4) | 0.6 (0.3–1.3) |
| | Q4 (0.019–0.130) | 1.7 (0.7–3.9) | 1.1 (0.4–2.8) | 1.1 (0.5–2.5) | 0.9 (0.4–2.3) | 1.4 (0.8–2.4) | 1.0 (0.5–1.9) |
| | p-value[d] | | 0.95 | | 0.83 | | 0.82 |
| Trans-nonachlor | Q1 (0.005–0.012) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.013–0.018) | 0.6 (0.2–1.6) | 0.6 (0.2–1.6) | 0.6 (0.3–1.4) | 0.7 (0.3–1.6) | 0.6 (0.3–1.2) | 0.6 (0.3–1.2) |
| | Q3 (0.019–0.027) | 1.3 (0.6–3.0) | 1.2 (0.5–2.9) | 0.7 (0.3–1.6) | 0.7 (0.3–1.7) | 0.9 (0.5–1.7) | 0.9 (0.5–1.6) |
| | Q4 (0.028–0.23) | 1.7 (0.7–3.8) | 1.2 (0.5–3.2) | 0.9 (0.4–1.9) | 0.8 (0.3–1.9) | 1.2 (0.7–2.1) | 0.9 (0.5–1.9) |
| | p-value[d] | | 0.40 | | 0.62 | | 0.88 |
| **Perfluoroalkyl substances** | | | | | | | |
| PFOA | Q1 (0.05–1.2) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (1.3–1.7) | 0.9 (0.4–2.0) | 0.9 (0.4–2.1) | 1.1 (0.5–2.3) | 0.9 (0.4–2.0) | 1.0 (0.5–1.7) | 0.9 (0.5–1.6) |
| | Q3 (1.8–2.5) | 0.9 (0.4–2.0) | 1.0 (0.4–2.2) | 0.9 (0.4–1.9) | 0.7 (0.3–1.6) | 0.9 (0.5–1.6) | 0.8 (0.5–1.5) |
| | Q4 (2.6–16) | 0.6 (0.2–1.6) | 0.9 (0.3–2.3) | 0.7 (0.3–1.6) | 0.7 (0.3–1.8) | 0.6 (0.3–1.2) | 0.8 (0.4–1.5) |
| | p-value[d] | | 0.86 | | 0.36 | | 0.44 |

**Table 3** (*continued*)

| Contaminant (μg/L) | | GDM (N=44) vs. Normal Glucose (N=1102)[a] | | Gestational IGT (N=49) vs. Normal Glucose (N=1102)[a] | | GDM or gestational IGT (N=93) vs. Normal Glucose (N=1102)[a] | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted OR[b] (95% CI) | Adjusted OR[c] (95% CI) | Unadjusted OR (95% CI) | Adjusted OR[c] (95% CI) | Unadjusted OR (95% CI) | Adjusted[c] OR (95% CI) |
| PFOS | Q1 (0.15–3.3) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (3.4–4.6) | 0.6 (0.3–1.5) | 0.6 (0.3–1.6) | 1.4 (0.6–3.0) | 1.2 (0.5–2.8) | 0.9 (0.5–1.7) | 0.9 (0.5–1.7) |
| | Q3 (4.7–6.8) | 0.9 (0.4–2.0) | 1.1 (0.5–2.5) | 1.4 (0.6–3.1) | 1.2 (0.6–2.8) | 1.1 (0.6–2.0) | 1.2 (0.6–2.1) |
| | Q4 (6.9–36) | 0.6 (0.2–1.4) | 0.7 (0.3–1.7) | 0.8 (0.3–2.0) | 0.8 (0.3–2.1) | 0.7 (0.4–1.3) | 0.7 (0.4–1.4) |
| | p-value[d] | | 0.70 | | 0.74 | | 0.59 |
| PFHxS | Q1 (0.1-0.66) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.67–1) | 1.4 (0.6–3.3) | 1.6 (0.7–3.8) | 3.5 (1.4–8.8) | 3.5 (1.4–8.9) | 2.2 (1.2–4.1) | 2.4 (1.3–4.4) |
| | Q3 (1.1–1.6) | 1.2 (0.5–2.8) | 1.4 (0.6–3.5) | 1.4 (0.5–4.1) | 1.3 (0.5–4.0) | 1.3 (0.6–2.5) | 1.3 (0.6–2.7) |
| | Q4 (1.7–40) | 0.8 (0.3–2.0) | 1.2 (0.4–3.5) | 2.4 (0.9–6.3) | 2.5 (0.9–7.0) | 1.4 (0.7–2.7) | 1.8 (0.9–3.6) |
| | p-value[d] | | 0.73 | | 0.44 | | 0.47 |
| **Polychlorinated biphenyls** | | | | | | | |
| PCB118 | Q1 (0.005–0.01) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.011–0.015) | 1.2 (0.5–2.9) | 1.0 (0.4–2.6) | 0.8 (0.4–1.8) | 0.8 (0.4–1.8) | 1.0 (0.5–1.8) | 0.9 (0.5–1.6) |
| | Q3 (0.016–0.022) | 1.3 (0.5–3.1) | 0.9 (0.3–2.5) | 0.7 (0.3–1.7) | 0.6 (0.3–1.6) | 0.9 (0.5–1.8) | 0.7 (0.4–1.4) |
| | Q4 (0.023–0.22) | 1.7 (0.7–4.0) | 1.4 (0.5–3.5) | 1.0 (0.5–2.2) | 0.9 (0.4–2.2) | 1.3 (0.7–2.3) | 1.1 (0.6–2.1) |
| | p-value[d] | | 0.55 | | 0.79 | | 0.90 |
| PCB138 | Q1 (0.005–0.017) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.018–0.026) | 2.0 (0.8–4.9) | 1.8 (0.7–4.8) | 0.6 (0.2–1.3) | 0.6 (0.3–1.4) | 1.0 (0.5–1.8) | 1.0 (0.5–1.8) |
| | Q3 (0.027–0.04) | 1.5 (0.6–3.9) | 1.3 (0.5–3.8) | 0.7 (0.3–1.5) | 0.7 (0.3–1.6) | 0.9 (0.5–1.7) | 0.9 (0.4–1.7) |
| | Q4 (0.041–0.43) | 1.9 (0.7–4.8) | 1.5 (0.5–4.2) | 0.8 (0.4–1.6) | 0.8 (0.3–1.8) | 1.1 (0.6–2.0) | 1.0 (0.5–1.9) |
| | p–value[d] | | 0.71 | | 0.60 | | 0.86 |
| PCB153 | Q1 (0.005–0.029) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.03–0.044) | 1.8 (0.7–4.4) | 1.9 (0.7–4.8) | 0.5 (0.2–1.2) | 0.6 (0.2–1.3) | 0.9 (0.5–1.7) | 0.9 (0.5–1.8) |
| | Q3 (0.045–0.07) | 1.1 (0.4–2.9) | 1.0 (0.3–3.0) | 0.6 (0.3–1.4) | 0.6 (0.2–1.4) | 0.8 (0.4–1.4) | 0.7 (0.4–1.4) |
| | Q4 (0.071–0.93) | 1.6 (0.7–4.0) | 1.4 (0.5–4.1) | 0.7 (0.3–1.4) | 0.7 (0.3–1.7) | 1.0 (0.5–1.7) | 0.9 (0.5–1.8) |
| | p-value[d] | | 0.82 | | 0.42 | | 0.65 |
| PCB180 | Q1 (0.005–0.019) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.02–0.03) | 1.4 (0.6–3.2) | 1.5 (0.6–3.8) | 0.6 (0.3–1.2) | 0.5 (0.2–1.3) | 0.9 (0.5–1.5) | 0.9 (0.5–1.6) |
| | Q3 (0.031–0.049) | 0.8 (0.3–2.0) | 0.7 (0.2–2.2) | 0.4 (0.2–1.0) | 0.4 (0.1–1.1) | 0.5 (0.3–1.1) | 0.5 (0.2–1.1) |
| | Q4 (0.05–1.1) | 1.3 (0.6–3.1) | 1.3 (0.5–3.5) | 0.7 (0.4–1.6) | 0.7 (0.3–1.8) | 1.0 (0.5–1.7) | 0.9 (0.5–1.8) |
| | p-value[d] | | 0.98 | | 0.48 | | 0.60 |
| Sum of all PCBs | Q1 (0.02–0.075) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.076–0.116) | 1.6 (0.7–3.7) | 1.4 (0.6–3.6) | 0.6 (0.3–1.3) | 0.6 (0.3–1.5) | 1.0 (0.5–1.7) | 0.9 (0.5–1.7) |
| | Q3 (0.117–0.179) | 0.8 (0.3–2.2) | 0.7 (0.2–2.0) | 0.5 (0.2–1.2) | 0.5 (0.2–1.2) | 0.6 (0.3–1.2) | 0.6 (0.3–1.1) |
| | Q4 (0.181–2.491) | 1.3 (0.5–3.0) | 1.0 (0.3–2.7) | 0.8 (0.4–1.6) | 0.8 (0.3–2.0) | 0.9 (0.5–1.7) | 0.8 (0.4–1.7) |
| | p-value[d] | | 0.60 | | 0.58 | | 0.43 |
| Sum of non-dioxin-like PCBs (138, 153, 180) | Q1 (0.015–0.065) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Q2 (0.066–0.1) | 1.8 (0.8–4.4) | 1.9 (0.7–4.7) | 0.6 (0.3–1.4) | 0.6 (0.3–1.5) | 1.0 (0.6–1.8) | 1.0 (0.5–1.9) |
| | Q3 (0.101–0.158) | 0.9 (0.3–2.5) | 0.8 (0.3–2.5) | 0.5 (0.2–1.2) | 0.5 (0.2–1.3) | 0.6 (0.3–1.2) | 0.6 (0.3–1.2) |
| | Q4 (0.159–2.46) | 1.6 (0.6–3.8) | 1.3 (0.5–3.8) | 0.8 (0.4–1.7) | 0.8 (0.3–2.1) | 1.0 (0.6–1.9) | 1.0 (0.5–2.0) |
| | p-value[d] | | 0.97 | | 0.65 | | 0.70 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Aroclor 1260 | Q1 (0.05–0.24) | 1 | | 1 | | 1 | | 1 | | 1 |
| | Q2 (0.25–0.37) | 1.6 (0.7–4.0) | | 1.5 (0.6–4.0) | | 0.6 (0.3–1.3) | | 0.6 (0.3–1.5) | | 0.9 (0.5–1.7) |
| | Q3 (0.38–0.58) | 1.4 (0.5–3.5) | | 1.2 (0.4–3.4) | | 0.5 (0.2–1.2) | | 0.5 (0.2–1.3) | | 0.7 (0.4–1.4) |
| | Q4 (0.59–7.1) | 1.6 (0.6–3.9) | | 1.3 (0.4–3.6) | | 0.7 (0.3–1.6) | | 0.8 (0.3–1.9) | | 0.9 (0.5–1.8) |
| | p-value[d] | | | 0.84 | | | | 0.46 | | 0.67 |

[a] Number of subjects with data for at least one exposure measurement and all covariates in addition to GDM and gestational IGT.
[b] OR = odds ratio.
[c] Adjusted for maternal age, race, pre-pregnancy BMI and education; analyses for organophosphorus pesticide metabolites are additionally adjusted for urinary specific gravity; analyses for PCBs and organochlorine pesticides are additionally adjusted for total lipids.
[d] p-value from linear test for trend across exposure categories.

statistical evidence of inverse associations between urine concentrations of two OP pesticide metabolites, DMP and DMTP, with GDM, and GDM and IGT combined. We found no consistent evidence of an association between levels of the other chemicals we examined and GDM or gestational IGT in the adjusted analyses.

The inverse associations we observed between DMP and DMTP with GDM are puzzling and, to our knowledge, have not been reported in previous studies. OP pesticides are hypothesized to increase the risk of diabetes through accumulation of acetylcholine leading to increased mobilization of glucose, but acetylcholine could also lead to increased insulin secretion in some cases, which would likely be protective against GDM (Rodriguez-Diaz et al., 2011), and hypoglycemia has been observed following exposure to OP pesticides in some experimental studies using animal models (Rahimi and Abdollahi, 2007). We cannot rule out the influence of residual confounding due to unmeasured protective factors, such as nutritional benefits from consumption of fruits and vegetables also associated with pesticide exposure, on the observed associations between maternal OP pesticide metabolites and GDM. A recent literature review found that the nutritional exposures showing the most salient relationships with increased risk of GDM were higher dietary fat and lower carbohydrate intakes (Morisset et al., 2010). While a protective effect of fruit and vegetable consumption for GDM has not been demonstrated, fruits and vegetables are likely to displace fat in the diet, as they are high fibre / high satiety foods. Furthermore, women who consume high levels of fruit and vegetables may also be at reduced risk for GDM due to other lifestyle variables that we did not measure, such as physical activity. The dietary measurements in the MIREC Study were not designed to measure fruit and vegetable consumption and included only select fruits and vegetables. Thus, we are unable to test the role that this potential bias may play in our findings.

The epidemiologic literature examining the association between OP pesticides and diabetes has primarily occurred in occupationally exposed populations. In one of the few cohort studies examining the association between pesticide exposure and GDM, self-reported exposure to two organophosphate pesticides (diazinon, phorate) during the first trimester were associated with an increased risk of GDM though the number of exposed cases was relatively small (Saldana et al., 2007). Another study also reported positive associations between OP pesticide exposure and incident diabetes among famers' wives (Starling, 2014) and among male farmers (Montgomery et al., 2008). Unlike the MIREC Study, these studies used self-reported data for both exposure and outcome assessments. Comparison of our results and these previous studies is challenged by differences in study sample (with MIREC being a primarily urban sample with low chronic exposure, primarily from the diet) and exposure assessment methods (biomarker vs. self-reported).

Not surprisingly, the OP pesticide metabolite concentrations in the MIREC cohort were lower than reported in residents or workers of agricultural communities. OP metabolite concentrations among MIREC participants were lower than reported in a cohort of pregnant women living in an agricultural community in California (Bradman et al., 2005), in a cohort of pregnant women without diabetes living in agricultural areas in Thailand (Kongtip et al., 2014), and in a cohort of Japanese workers with environmental or occupational exposures to OPs (Ueyama et al., 2012). Thus, the lower concentrations in the MIREC study may contribute to differences in the observed results and positive associations reported in occupationally exposed populations. When compared to non-agricultural cohorts, OP pesticide metabolite concentrations were similar or higher in the MIREC cohort compared to other general population cohorts (Berman et al., 2013). Concentrations of OP pesticide metabolites in our study were higher than reported in the U.S. NHANES (Barr et al., 2011).

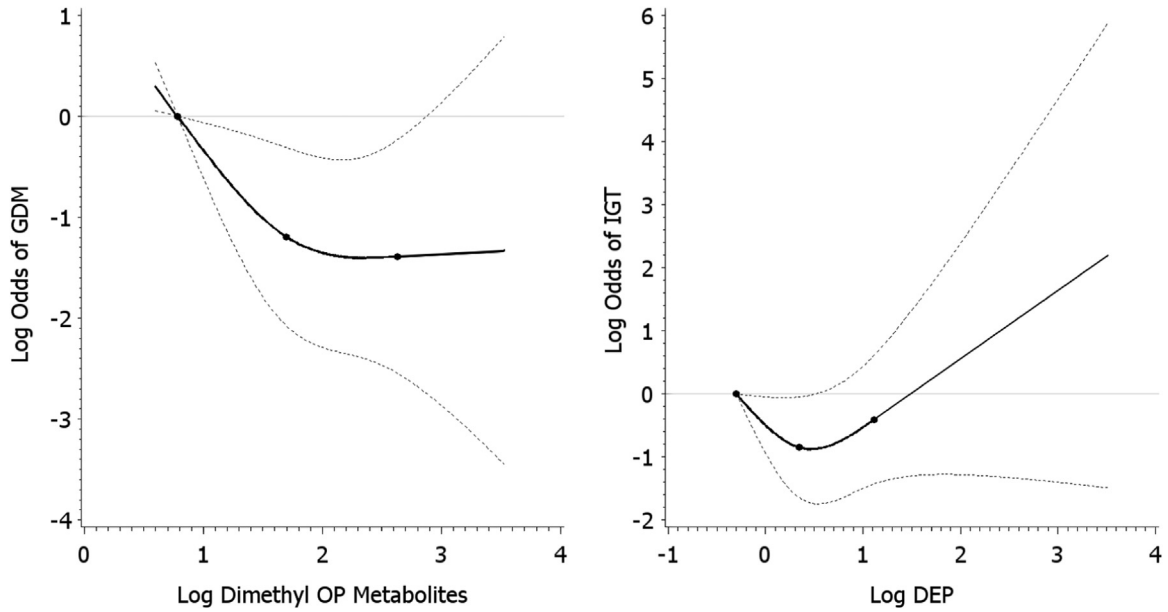


**Fig. 1.** Restricted spline curve associations between $\log_{10}$ organophosphorus pesticide metabolites and log odds of study outcomes, adjusted for maternal age, race, pre-pregnancy BMI, education and urinary specific gravity. Knots were located at the 5th, 50th and 95th percentiles. Dashed lines = 95% CI; dots = knots.

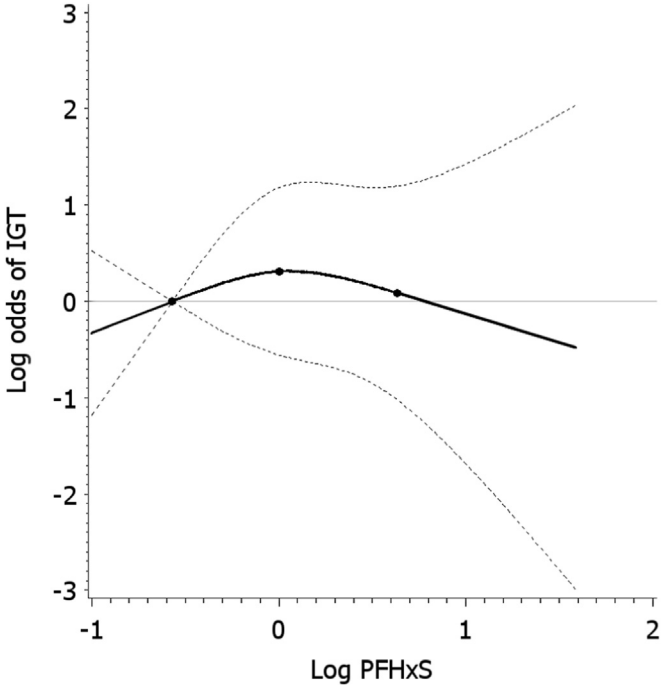


**Fig. 2.** Restricted spline curve association between $\log_{10}$ PFHxS (μg/L) and log odds of gestational IGT, adjusted for maternal age, race, pre-pregnancy BMI and education. Knots were located at the 5th, 50th and 95th percentiles. Dashed lines = 95% CI; dots = knots.

Concentrations of DMTP were higher in MIREC participants than among women age 20–39 in Cycle 1 of the Canadian Health Measures Survey (CHMS), while levels of DEP and DMP were similar between the two studies (Health Canada, 2010).

Literature regarding associations between the other chemical classes measured in this study and diabetes among pregnant populations is scarce. Studies that have examined potential associations between diabetes and exposure to organochlorine pesticides, PCBs, and PFASs have largely focused on type 2 diabetes or self-reported diabetes. For example, positive associations between OC pesticides and diabetes have been identified in U.S. NHANES (Everett and Matheson, 2010; Lee et al., 2006), the Hispanic Health and Nutrition Study (Cox et al., 2007), a Helsinki cohort study (Airaksinen et al., 2011), and a cross-sectional analysis of Great Lakes sport fish consumers (Turyk et al., 2009b). In contrast, null or negative results have also been reported between OC pesticides and diabetes (Gasull et al., 2012; Wu et al., 2013).

Literature regarding the association between PFAS exposure and diabetes is equivocal, with cohort (Leonard et al., 2008; Lundin et al., 2009) and cross-sectional analyses (Lin et al., 2009) reporting both positive (Leonard et al., 2008; Lundin et al., 2009) (Lin et al., 2009) and negative or null findings (Karnes et al., 2014; Lind et al., 2014; MacNeil et al., 2009; Nelson et al., 2010). A recent study of PFAS exposure and GDM found a positive association for PFOA, with no significant associations found for six other PFASs (Zhang et al., 2015). While we did not find statistical evidence of associations between PFASs and our study outcomes in cubic spline models, results from our regression analysis on PFHxS and gestational IGT are consistent with a low-dose effects hypothesis. Associations between low doses of other persistent organic pollutants have been reported with incident diabetes (Lee et al., 2010) and metabolic precursors to diabetes (Lee et al., 2011).

PCB exposure has been found to be associated with diabetes though, to our knowledge, no identified study has focussed on prenatal exposure and GDM. Analysis from a pregnancy cohort of similar size to the MIREC Study showed a dose-response relationship between total serum PCBs and prevalent diabetes, though authors did not show results separately for GDM (Longnecker et al., 2001). A cross-sectional study of 40 pregnant women without diabetes found that PCB concentration was associated with reduced insulin sensitivity after adjustment for age and pre-pregnancy BMI (Chen et al., 2008). PCBs examined in one study were also associated with markers of insulin in women with a history of GDM (Arrebola et al., 2015).

It is plausible that the lack of positive association between these contaminants and GDM in the present study stems from low overall exposure levels in the MIREC cohort. The OC pesticide concentrations in our study are substantially lower than in studies that found associations with type 2 diabetes (Cox et al., 2007; Lee et al., 2011a, 2010; Philibert et al., 2009; Porta et al., 2012; Rignell-Hydbom et al., 2009; Son et al., 2010; Turyk et al., 2009b). Our observed concentrations of DDE were also slightly lower than

those for women of childbearing age in the CHMS, while concentrations of oxychlordane and trans-nonachlor were similar between the two studies (Health Canada, 2010).

Plasma PFAS concentrations were lower in the MIREC cohort than in most of the studies we reviewed (Fei et al., 2007; Lin et al., 2009; Lind et al., 2014; MacNeil et al., 2009; Melzer et al., 2010; Nelson et al., 2010). PCB levels were also several times lower in our study compared to other population-based samples (Gasull et al., 2012; Lee et al., 2010; Porta et al., 2012). Our observed PCB concentrations were similar or lower than those measured in a US cohort (Sexton et al., 2013) and in the CHMS (Health Canada, 2010).

### 4.1. Strengths and limitations

There were a substantial number of subjects for whom a GCT was not performed and who were therefore excluded from our analyses, reducing statistical power. However, given the small magnitude of the differences between included and excluded participants on demographic variables, we do not expect that our findings would be strongly affected by selection bias. It should be acknowledged that findings from the regression analyses are based on small numbers of cases in each quartile. Therefore, some of our negative findings may be due to type 2 error. Additionally, while we were able to adjust for a wide range of potential confounding variables, there remains a possibility of residual confounding by dietary intake or other factors not measured. Specifically, data were not collected on the presence of diabetes in relatives of MIREC Study participants, and family history of diabetes may constitute an unmeasured confounding variable. In light of the observed correlations across exposure classes and the exploratory nature of our study, we examined only individual exposures and chemical classes. Future work should explore the impact of sums of different types of exposures.

An important limitation of our analysis is the use of a single urinary measure for OP pesticide metabolites. As these chemicals have short elimination half-lives (Lambert et al., 2005; Lu et al., 2008; Rauch et al., 2012), within-person reliability in urinary OP metabolite concentrations has been reported as weak to moderate, with intraclass correlation coefficients ranging from 0.21 to 0.33 for the metabolites that we examined (Spaan et al., 2015). Thus our use of a single measurement may not reflect overall exposure in pregnancy. Future studies incorporating multiple measurements are needed to better illuminate variation in levels and effects of OP pesticides across pregnancy.

The MIREC study sample exhibits a low-risk socioeconomic profile in terms of education, nativity, smoking and marital status, compared to the overall Canadian population giving birth at the time the MIREC participants were recruited (Arbuckle et al., 2013). Our results therefore may have limited generalizability to other populations with differing socioeconomic characteristics and exposure patterns, particularly those with occupational exposure to the chemicals we examined. Along these lines, our analyses were limited to chemical exposures for which there were detectable levels in $>75\%$ of subjects. This resulted in the exclusion of several chemicals assessed in the MIREC Study, including three OP pesticide metabolites, eight OC pesticides, and 20 PCBs. Further study of these chemicals in relation to diabetes may be warranted, particularly in areas with higher concentrations.

These limitations must be weighed against several important strengths of our study, including the prospective study design and the comprehensive questionnaire data and anthropometric measurements collected in the MIREC Study, which enabled us to control for a rich variety of potential confounding variables. We also measured our study outcomes from medical charts using standard guidelines, rather than relying on self-reported outcome measures.

## 5. Conclusions

Using a prospective cohort design, we evaluated the relationships between OP and OC pesticides, PFASs, and PCBs measured during the first trimester of pregnancy with risk of being diagnosed with GDM or gestational IGT based on published national guidelines. Though we did not find consistent evidence for any positive associations between the chemicals we examined and GDM or gestational IGT, we observed strong inverse associations between dimethyl OP pesticide metabolites and GDM. These findings require further investigation in other populations.

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All participants in this study signed informed consent forms, and the study received ethical approval from Health Canada and all the study centres.

The authors declare they have no actual or potential competing financial interests.

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